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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
ARTHUR, L	
ART UNIT	**PAPER NUMBER**
1655	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev.11/00)

1- File Copy

Office Action Summary	Application No. 09/448,042	Applicant(s) LAPIDUS ET AL.	
	Examiner Lisa B. Arthur	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,10-12,15-20 and 22-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,4,10-12,15-20 and 22-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. This action is in response to the paper filed July 16, 2001. Currently, claims 1,4,10-12,15-20 and 22-24 are pending. All of the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance for the reasons which follow. Any rejections which have not been reiterated have been obviated by the amendments made to the claims. This action contains new grounds of rejection. Applicant should note that the examiner handling this application has changed.

NEW GROUNDS OF REJECTION

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 10 is indefinite because the claim is in an improper Markush format. The claim uses the language "selected from the group consisting of A, B, C or D. However, a Markush grouping either needs to be specified as "selected from the group consisting of A,B,C, and D" or "selected from A,B,C, and D".

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. Claims 1, 4, 10, 12, 15, 16,18, 20 and 24 are rejected under 35 U.S.C. 102(a) as being anticipated by Kwok et al. (U.S. Pat 5,945,283). Kwok et al. teaches a method for determining the presence of a target nucleotide by adding to a DNA sample a primer convalently labeled with a fluorescent dye, performing primer extension in presence of a dideoxynucleotide covalently labeled with a fluorescent dye capable of being activated through fluorescent energy transfer to produce a detectable fluorescent signal when the dideoxynucleotide is incorporated into the extension product, determining the presence of the fluorescent signal and thereby determining the presence of the target nucleotide (see abstract, Figure 1, column 3; lines 21-33 and examples 1-2). Kwok et al. Teaches the limitation of claim 4 by teaching that the extension reaction could be performed in the presence of at least two different dideoxynucleotides (see example 5, column 21, line 40 through column 23). Kwok et al. Teach the limitation of claim 10 by teaching the use of 6-carboxy-X rhodamine, N,N,N,N-tetramethyl-6-carboxyrhodamine, 6-carboxy-X-rhodomine, and fluorescein (Table 1) and teaches that any number of fluorophore combination can be use in their method (column 7, lines 52-60). Kwok et al. Teach the use of their method to detect a nucleic acid mutation (see examples 4 and 5) (limitation of claim 18) and to detect a single nucleotide polymorphism (see example 2) (limitation of claim 20) and teaches a situation in which the target nucleotide is absent (see Figure

1) (limitation of claim 24). Therefore, Kwok et al. teach every limitation recited in the claims.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok et al. in view of Lee et al. (U.S. Pat 5, 945,526).

Kwok et al. teaches a method for determining the presence of a target nucleotide by adding to a DNA sample a primer covalently labeled with a fluorescent dye, performing primer extension in presence of a dideoxynucleotide covalently labeled with a fluorescent dye capable of being activated through fluorescent energy transfer to produce a detectable fluorescent signal when the dideoxynucleotide is incorporated into the extension product, determining the presence of the fluorescent signal and thereby

determining the presence of the target nucleotide (see abstract, Figure 1, column 3; lines 21-33 and examples 1-2). Kwok et al. teaches the limitation of claim 4 by teaching that the extension reaction could be performed in the presence of at least two different dideoxynucleotides (see example 5, column 21, line 40 through column 23). Kwok et al. teach the limitation of claim 10 by teaching the use of 6-carboxy-X rhodamine, N,N,N,N-tetramethyl-6-carboxyrhodamine, 6-carboxy-X-rhodomine, and fluorescein (Table 1) and teaches that any number of fluorophore combinations can be use in their method (column 7, lines 52-60).

Kwok et al. does not specifically identify 6-carboxyfluorescein as a fluorophore for use in an energy transfer reaction.

However, Lee et al. teaches that 6-carboxyfluorescein is a known fluorophore which functions energy transfer reactions (see column 23, lines 12-14). Lee et al. also teach labeling dideoxynucleotides with these fluorophores (column 7 , lines 45-54). It is also noted that Lee et al. teach the Cy5 fluorescent dye as an energy transfer label (column 23, line 36).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kwok et al. to include the use of the fluorophore 6-carboxy-fluorescein as taught by Lee et al. in order to make the claimed invention as a whole because Kwok et al. taught that a number of different fluorophores could be used in their method and because Lee et al. specifically taught that 6-carboxy fluorescein was useful as an energy transfer fluorophore which

would have been expected to have functioned in an equivalent manner to the fluorophores of Kwok et al.

8. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok et al. in view of Gillespie (5,483,834).

Kwok et al. teaches a method for determining the presence of a target nucleotide by adding to a DNA sample a primer covalently labeled with a fluorescent dye, performing primer extension in presence of a dideoxynucleotide covalently labeled with a fluorescent dye capable of being activated through fluorescent energy transfer to produce a detectable fluorescent signal when the dideoxynucleotide is incorporated into the extension product, determining the presence of the fluorescent signal and thereby determining the presence of the target nucleotide (see abstract, Figure 1, column 3; lines 21-33 and examples 1-2).

Kwok et al does not teach obtaining the nucleic acid from a stool sample. However, Gillespie teaches a method of obtaining nucleic acid and performing hybridization assays for detection of target nucleotide sequences from heterogenous biological samples such as stool samples (see column 7, lines 65-67, column 59, example 14).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Kwok et al. to a patient stool sample in order to make the claimed invention as a whole because Gillespie taught that a stool sample is a well known biological sample known to contain

cellular material and nucleic acids and because Gillespie taught a method for extracting the nucleic acid from a stool sample such that it could be effectively analyzed by nucleic acid hybridization type methods such as the one of Kwok et al. The ordinary artisan would have been motivated to have analyzed a stool sample using the method of Kwok et al. because a stool sample can be easily obtained by non-invasive techniques.

9. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok et al. in view of Lu et al. (abstract)

Kwok et al. teaches a method for determining the presence of a target nucleotide by adding to a DNA sample a primer covalently labeled with a fluorescent dye, performing primer extension in presence of a dideoxynucleotide covalently labeled with a fluorescent dye capable of being activated through fluorescent energy transfer to produce a detectable fluorescent signal when the dideoxynucleotide is incorporated into the extension product, determining the presence of the fluorescent signal and thereby determining the presence of the target nucleotide (see abstract, Figure 1, column 3; lines 21-33 and examples 1-2).

Kwoh et al. does not specifically teach applying the method to the detection of mutations in the p53, apc, or ras genes. However, Lu et al. teach that the p53, apc and ras genes are all known to be oncogenes involved in a number of different cancers.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have applied the nucleotide detection method of Kwok et al. to the detection of mutations in p53, apc and ras because Lu et al. taught

that these genes were known to be involved in cancer and that the detection of mutations was important for the diagnosis and prognosis of cancer.

10. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok et al. in view of O'dell et al. (Clin. Chem. (1998) 44(1): 183-185.

Kwok et al. teaches a method for determining the presence of a target nucleotide by adding to a DNA sample a primer covalently labeled with a fluorescent dye, performing primer extension in presence of a dideoxynucleotide covalently labeled with a fluorescent dye capable of being activated through fluorescent energy transfer to produce a detectable fluorescent signal when the dideoxynucleotide is incorporated into the extension product, determining the presence of the fluorescent signal and thereby determining the presence of the target nucleotide (see abstract, Figure 1, column 3; lines 21-33 and examples 1-2).

Kwok et al. does not teach using a sample from a pooled patient population. However, O'dell et al. taught a method of analyzing a target nucleic acid for the presence of mutations associated with disease by screening pooled DNA samples.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Kwok et al. to screening of pooled DNA samples as taught by O'dell et al. because O'dell et al. taught that screening pooled DNA samples allowed the efficient and cost-effective processing of a large number of specimens.

11. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok et al. in view of Gillespie as applied to claim 17 above, and further in view of O'dell et al.

Neither Kwok et al. or Gillespie teach use of their method to screen pooled patient samples. However, O'dell et al. taught a method of analyzing a target nucleic acid for the presence of mutations associated with disease by screening pooled DNA samples.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Kwok et al. in view of Gillespie to screening of pooled DNA samples as taught by O'dell et al. obtained from stool because O'dell et al. taught that screening pooled DNA samples allowed the efficient and cost-effective processing of a large number of specimens.

12. No claims are allowable over the prior art.

13. Applicant should note that the examiner handling this application has now been changed. Any inquiry concerning this communication or earlier communications from the examiner should be now directed to Lisa B. Arthur whose telephone number is 308-3988. The examiner can normally be reached on Monday-Wednesday from 7:00 am to 2:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone

number for the organization where this application or proceeding is assigned is 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 308-0196.

Lisa B. Arthur
Primary Examiner
Art Unit 1655